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SHORT COMMUNICATION

Long-term, low-dose erythromycin in bronchiectasis subjects with frequent infective exacerbations

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Background: Macrolide antibiotics are increasingly prescribed for subjects with non-cystic fibrosis (CF) bronchiectasis, an empiric extension of their proven efficacy in CF. Widespread, injudicious use of long-acting macrolides, particularly azithromycin, risks significantly increasing population antimicrobial resistance.

Methods: In an attempt to power a definitive randomised-controlled trial (RCT), an uncontrolled evaluation of the impact of long-term, low-dose oral erythromycin therapy upon pulmonary exacerbation frequency in non-CF bronchiectasis subjects was performed. Adult bronchiectasis subjects with at least 2 infective exacerbations in the preceding 12 months were followed for 12 months following commencement of prophylactic oral erythromycin 250 mgs daily. The co-primary outcome measures, comparing the 12 month erythromycin and pre-erythromycin periods, were numbers of infective exacerbations and days of antibiotic therapy for infective exacerbations.

Results: In the 24 evaluable subjects completing a minimum of 12 months of therapy, erythromycin was associated with halving of both the median (range) annual number of infective exacerbations (2 (0–8) vs 4 (2–11), 95% CI 1.5 to 3.5, $p < 0.0001$) and annual days of antibiotic use (21 (0–78) vs 44 (15–138), 95% CI 18 to 40, $p < 0.0001$) compared with the preceding 12 month period. **Conclusions:** Low-dose erythromycin may have a robust effect upon exacerbation frequency in non-CF bronchiectasis subjects with frequent exacerbations and this warrants proceeding to a definitive intervention study. These data have enabled powering of an RCT of long-term, low-dose erythromycin, which is now underway and also incorporates bronchoscopic evaluation for pathophysiological data.

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Non-cystic fibrosis (CF) bronchiectasis has failed to attract the profile and research expenditure of its more fashionable cousin, CF and much of the therapy employed for subjects with bronchiectasis is simply extrapolated from CF management. However, where randomised-controlled trials of proven CF therapies have been conducted in bronchiectasis subjects, they have shown negative, even deleterious, results.^{1–3} Azithromycin is increasingly being used empirically in the management of bronchiectasis in the clinic with open-label studies suggesting benefit.^{4–6} However, there are significant risks associated with more widespread use of long-acting macrolides,⁷ particularly antimicrobial resistance. Azithromycin persists at subinhibitory concentrations for prolonged periods (up to 30 days⁸) and has the propensity to rapidly induce antibiotic resistance (potentially to β -lactams in addition to macrolides).⁹ A single 3 day course of azithromycin increases the proportion of macrolide-resistant streptococci by up to 53% compared with placebo⁹ and the increasing prevalence of macrolide-resistant *Streptococcus pneumoniae* strains in Portugal has been linked to increasing azithromycin prescription between 1999 and 2002.¹⁰ The establishment of azithromycin therapy for non-CF bronchiectasis has the very real potential to be empirically extended even further into widespread chronic maintenance therapy for patient with 'chronic lung conditions', with substantial risks to population antimicrobial resistance. Erythromycin potentially offers macrolide immunomodulatory benefits with a lower risk of resistance induction¹¹ and one prior study in bronchiectasis adults has shown improvements in sputum volume and lung function.¹²

In order to obtain powering data for an RCT of long-term, low-dose erythromycin therapy, we evaluated the effects of open-label erythromycin upon exacerbation frequency and antibiotic use in frequent 'exacerbators' with non-CF bronchiectasis.

Subjects were recruited from the Respiratory Medicine Department of the MaterAdult Hospital, a tertiary metropolitan teaching hospital that also includes the regional adult CF unit. Subjects aged 25 to 85 years had a diagnosis of bronchiectasis confirmed on high-resolution computed tomographic (HRCT) scan of the chest, had daily chronic sputum production, had experienced a minimum of 2 infective pulmonary exacerbations requiring antibiotic therapy in the preceding 12 months and had no treatable cause for recurrent exacerbations. Exclusion criteria included current smoking, macrolide therapy within the prior 3 months, culture of mycobacterial organisms, concomitant medications with the substantial for important interactions with erythromycin and any non-respiratory

disease with the potential to result in death in the subsequent 12 months. Initiation or cessation of respiratory medications during the 12 month treatment period resulted in exclusion of data.

Subjects were commenced upon 250 mgs daily of erythromycin base (given as 400 mgs of erythromycin ethylsuccinate), reviewed 1 month after commencement and then at intervals according to clinical need for the remainder of the 12 month period. The co-primary outcome measures were the number of pulmonary exacerbations requiring antibiotics (both oral and intravenous) per patient per year and the total days of antibiotics per person per year, comparing the 12 months of erythromycin therapy with the immediately preceding 12 month period. Patients' reported rescue antibiotic use was independently verified for all subjects by obtaining and reviewing pharmacy and medication prescription records from both the hospital pharmacy and patients' private pharmacies. Only subjects completing at least 12 months of uninterrupted therapy were included in the per protocol analysis. Data were analysed using Wilcoxon's signed ranks test and measures of effect are reported with 95% confidence intervals (CI).

Twenty-nine (29) subjects commenced long-term erythromycin therapy however one subject died (severe chronic hypercapneic respiratory failure at enrolment and died of progressive respiratory failure, after 6 months), one subject was non-compliant, two subjects withdrew (one developed nausea, one headache) and one subject was lost to follow-up. Complete follow-up data were available for all 24 remaining subjects. Three of these subjects commenced inhaled colistin therapy during the intervention period and their data have been excluded, leaving 21 per protocol subjects (15 female, mean \pm SD age 62.5 ± 11 years, FEV₁ percent predicted $65.5 \pm 26.2\%$). *Pseudomonas aeruginosa* was cultured from sputum in 9 subjects, *Haemophilus influenzae* in 3, *Moraxella catarrhalis* in 1, *Aspergillus fumigatus* in 1 and normal flora in 7.

Erythromycin therapy was associated with highly significant, greater than 50% reductions in both co-primary outcomes (see Table 1). No subject cultured new respiratory pathogens at the completion sample and no erythromycin resistant organisms emerged during the study, although 6 subjects who had initially cultured pathogens (2 *P. aeruginosa*, 2 *H. Influenzae*, 1 *M. catarrhalis*, 1 *A. fumigatus*) cultured normal flora only. Side-effects were reported by only the two subjects who ceased the drug (one nausea and one headache); liver function tests remained normal in all subjects.

These uncontrolled data suggest that long-term, low-dose erythromycin therapy may have a potent effect upon

Table 1 Comparison of outcomes in the pre-erythromycin and erythromycin periods* (Per protocol group, $n = 21$).

	Pre-erythromycin	Erythromycin	95% CI	P value
Total antibiotic courses	4 (2–11)	2 (0–8)	1.5 to 3.5	<0.0001
Total days of antibiotics	44 (15–138)	21 (0–78)	18 to 40	<0.0001
Intravenous courses of antibiotics	0 (0–3)	0 (0–1)	0 to 1	0.0078
Oral courses of antibiotics	3 (1–11)	1 (0–8)	1 to 3	<0.0001
FEV ₁ (SD)	1.67 (0.72)	1.80(0.74)	–0.29 to 0.12	0.39

(Data are presented as median (range) unless otherwise indicated; * representing the 12 months immediately preceding and following commencement of erythromycin).

exacerbation frequency in non-CF bronchiectasis subjects. The reduction in exacerbations was clinically meaningful and was consistent across patients with only one subject showing an increase in exacerbation frequency. Furthermore, the magnitude of effect ($\geq 50\%$ reduction in exacerbation frequency) is similar to that previously reported for azithromycin therapy.^{4–6}

A number of recent reviews have highlighted the need for RCT's that address the efficacy of therapies, including macrolides, in bronchiectasis.^{7,13} The current data provided both powering data and strong impetus for a prospective clinical study and we have subsequently commenced a double-blind, placebo-controlled RCT, the Bronchiectasis and Low-Dose Erythromycin Study (BLESS). Sample size calculations for BLESS were based upon more modest estimates of baseline exacerbation frequency¹² and treatment effect than the current study, showing that 98 subjects give 90% power to show a 28% reduction in annual exacerbation frequency at the 5% significance level. Numbers have been increased to allow for dropout.

The potential for development of antibiotic resistance with long-term antibiotic therapy is a critical issue that needs to be carefully weighed against potential benefits, notwithstanding the lesser risk associated with erythromycin than the long-acting macrolides. Seemungal et al found little evidence of development of erythromycin resistance in sputum pathogens with 12 months of erythromycin therapy in COPD subjects.¹⁴ However the development of macrolide resistance within identified respiratory pathogens is not the greatest concern, particularly in bronchiectasis subjects whose dominant respiratory pathogens are rarely constitutively macrolide susceptible anyhow. Instead, the primary risk of resistance induction with long-term antibiotic use relates to commensal organisms, particularly oropharyngeal streptococci, which can then be transmitted between individuals within the community with subsequent effects upon population resistance. Hence, in the subsequent BLESS RCT, macrolide susceptibility of oropharyngeal flora forms a key outcome measure, performed using the methods described by Malhotra-Kumar et al.⁹

The daily dose of erythromycin selected for the current study (250 mgs of erythromycin base) is lower than that described in prior studies in DPB (400–600 mg),¹⁵ COPD (500 mgs)¹⁴ or bronchiectasis (1000 mgs).¹² The current data support the selection of this low-dose, which minimises the potential for side-effects.

The exact mechanism/s by which macrolides exert beneficial effects in CF and DPB are unclear. Of relevance to the chronic suppurative airways diseases, demonstrated effects include inhibition of neutrophil elastase,¹⁶ reductions in IL-8 expression and release from epithelial cells^{17,18} and attenuation of both mucin synthesis and mucus secretion.^{19,20} However, human studies evaluating the potential *in vivo* immunomodulatory mechanisms of action of macrolides have been limited to evaluations of blood and respiratory secretions and there is a need for more detailed mechanistic data in humans. The BLESS study includes a bronchoscopy study subgroup that will provide important mechanistic and pathophysiologic data via endobronchial biopsies. The current data are the catalyst for clinical research that we hope will inform our understanding and future management of not only non-CF bronchiectasis, but

also respiratory immunomodulatory therapy with macrolide antibiotics.

Conflict of interest statement

DJS has received honoraria for serving on the advisory boards of Pharmaxis and Phebra, but has no other conflict of interest to declare. MM has no conflict of interest to declare.

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